**Histamine as a Potential Therapeutic Target for**

**Preventing COVID-19 Progression to ARDS**

Michael Johnson PA-C, 4/8/2020

***Hypothesis: Histamine is a major role player in progression of heightened immune response that can result in ARDS and “cytokine storm” in certain individuals infected with COVID-19. We can augment the response by blocking the proinflammatory effects at H1 receptors which will free up a higher percentage of the histamine to bind to immune system dampening H2 receptors. This will result in decreased inflammation and oxidative damage to the surrounding tissue. It will protect the cells and tissue from an otherwise unchecked and ever- increasing cytokine-mediated inflammatory cascade. Levocetirizine is an ideal drug candidate to accomplish this.***

**Background:**

**By all accounts thus far, COVID-19 becomes most lethal when the human immune response causes an excessive tissue damaging immune response – this is what is most responsible for the Acute Respiratory Distress Syndrome that damages the lungs so badly that we have to treat some patients with ventilators. Many have pushed the concept that certain individuals can develop a “cytokine storm”, which happens when an excessive amount of proinflammatory cytokines result in ever-increasing and unchecked inflammation, oxidative cell injury, and cell death. This can quickly lead to steadily worsening ARDS, septic shock, multi-organ failure, and death. This is further supported by a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, that demonstrated elevated IL-6 (p<0.0001) and elevated ferritin (p<0.001) are very strong predictors of fatality[[1]](#endnote-1). Some doctors are trying to treat people with the disease with the blanket response of using powerful anti-inflammatory drugs to try and slow or stop the process but there is concern that suppressing the body’s immune system at the same time that the body is trying to fight off the deadly virus is dangerous. My proposal is that dampening the effects of endogenously released histamine through H1 blockers can help prevent the progression to ARDS or a “cytokine storm”. A safety valve to help prevent the immune system from destroying you if you need it would be far better, safer, and have the most opportunity to treat as many people as possible.**

**Alveolar macrophages (AMs) are the most abundant cells in the airway lumen and play a crucial role in determining the development of immune responses, Th1/Th2, in the lungs:**

1. AMs produce both Th1(IL-12) and Th2(IL-10 and IL-13) cytokines.[[2]](#endnote-2) [[3]](#endnote-3)
2. AMs secrete a panoply of mediators, including TNF, IL-1, IL-6, IL-8, and NO. [[4]](#endnote-4) [[5]](#endnote-5) [[6]](#endnote-6)
	1. TNF plays a pivotal role in inflammation by stimulating inflammatory cells and increasing production of cytokines such as IL-1, IL-6, IL-8, and IL-12.[[7]](#endnote-7)

**Histamine plays contradictory roles in immune cell-driven inflammation in the lungs:**

1. Histamine releases proinflammatory IL-6 by lung macrophages via H1 receptor activation[[8]](#endnote-8) [[9]](#endnote-9).
2. Histamine has been shown to stimulate release of hydrogen peroxide by primary bronchial epithelial cells via H1 receptor signaling[[10]](#endnote-10).
3. Histamine increases pulmonary edema via H1, even in absence of perfusion**[[11]](#endnote-11).**
4. Histamine dampens the immune response by inhibiting chemotaxis, phagocytosis, and production of TNF-alpha and superoxide anion via H2 receptor activation[[12]](#endnote-12) [[13]](#endnote-13) [[14]](#endnote-14).
	1. TNF-alpha contributes to progression of inflammation via enhancement of expression of adhesion molecules on microvascular endothelium and stimulation of chemotaxis and activation of neutrophils, which release ROS, proteolytic enzymes, and additional cytokines[[15]](#endnote-15) [[16]](#endnote-16) [[17]](#endnote-17)
	2. Superoxide anion (O2-) is the main player in Reactive Oxygen Species (ROS) which are primary drivers of tissue damage associated with inflammation. Superoxide Dismutase (SOD) converts ROS into hydrogen peroxide which are then removed by glutathione peroxidase or catalase.

**Selective H1 receptor blockade can drive the histamine mediated immune response to decrease inflammation and oxidative damage.**

1. Blocking H1 receptors will decrease the release of proinflammatory IL-6 by lung macrophages.
2. Less hydrogen peroxide will be produced at the site of inflammation.
3. Less pulmonary edema (even if tissue perfusion is hampered from injury).
4. More histamine will be available to bind to H2 receptors as they are not binding to H1 receptors, resulting in:
	1. Decreased production of TNF-alpha (resulting in a decreased inflammatory cascade)
	2. Decreased production of superoxide anion (resulting in less oxidative damage to lung tissue)

**Levoceterizine is an ideal drug candidate for trial**

1. Levocetirizine has been objectively established as the most potent of the five modern generation antihistamines through histamine induced wheal and flare data.
	1. Lower volume of distribution
	2. Greater histamine receptor affinity in an inflamed state (low pH)
	3. Greater receptor occupancy at 24 hours with physiologic doses.
2. Third-generation H-1 antihistamine (least likely to cause drowsiness)
3. Few side effects (available OTC)
4. Once daily dosing: 5 mg daily (2.5 mg for renal patients), can reach steady state in <24 hours if given twice during the first day (Q12 hours x 2, then Q24 hours)
5. Readily available and cheap (Generic and OTC)

**Research Supports the Use of Levocetirizine to Decrease Inflammation in a Rat Lung Injury Study[[18]](#endnote-18):**

Levocetirizine Pretreatment Mitigates Lipopolysaccharide-Induced Lung Inflammation in Rats

*Alaa N. A. Fahmi, George S. G. Shehatou, and Hatem A. Salem,* Biomed Res Int. 2018 Aug 13. 7019759

1. Currently, we have very limited knowledge on treatment of COVID-19. However, this study uses a well established method to cause lung inflammation/injury and the immune response should be similar. Lipopolysaccharide(LPS)-elicited lung injury in rats results in similar leukocyte infiltration, lung edema, abnormal gas exchange, and mortality that we see in humans with ARDS[[19]](#endnote-19).
2. The rats were randomly assigned into 3 groups of 6 rats. One group received levocetirizine daily for a week and the other 2 groups did not. On day 8, the levocetirizine group and the second group received LPS through intraperitoneal injection, the third group was a control group and they did not receive LPS. 18 hours after injection of LPS, blood was collected and serum was separated for measurement of c-reactive protein. The chest was surgically opened at midline and bronchoalveolar lavage fluid (BALF) was collected. The lungs were removed for assessment of lung water content and histopathological examination. In a separate series of experiments, left lungs were removed and homogenized and centrifuged with supernatants collected for assessment of oxidative status and TNF-alpha.
3. This study shows LPS injured rats have significant inflammation, oxidative injury, and histopathologic injury under the microscope when comparing to control group. This confirms the validity of using LPS injection as a model to study lung inflammation/injury. LPS injury in comparison to control group shows:
	1. Marked elevation of CRP (P<0.0001)
	2. Increased edema demonstrated through lung wet/dry ratio (P<0.001)
	3. Increased BALF protein content and total cell count (P<0.05)
	4. Increased BALF lactate dehydrogenase (LDH) activity and nitrite/nitrate (P<0.05, P<0.0001)
	5. Increased oxidative stress
		1. Increased malondialdehyde (P<0.01)
		2. Decreased glutathione (P<0.0001)
		3. Decreased superoxide dismutase activity (P<0.001)
	6. Increased TNF-alpha in the BALF and lung homogenates (P<0.0001, P<0.001)
	7. Marked deterioration of total lung injury score (from 0-2 to 9-14, P<0.01)
4. This study showed significant attenuation of markers of inflammation, lung edema, oxidative injury, and histopathologic injury under the microscope when comparing the group treated with Cetirizine and LPS injection versus the group with just LPS injection:
	1. Marked decrease of CRP(P<0.0001)
	2. Decreased lung wet/dry weight ratio (P<0.05)
	3. Decreased BALF protein content and total cell count (P<0.05)
	4. Decreased BALF lactate dehydrogenase(LDH) activity and nitrite/nitrate (P<0.05, P<0.05)
	5. Decreased oxidative stress
		1. Decreased malondialdehyde (P<0.05)
		2. No statistical difference with glutathione
		3. Increased superoxide dismutase activity (P<0.05) (this breaks down superoxide anion, resulting in less oxidative damage to surrounding cells)
	6. Decreased TNF-alpha in the BALF and lung homogenates (P<0.05, P <0.05)
	7. Marked improvement of lung injury scores (from 9-14 to 2-4, P<0.05)
5. If you take nothing away from this study but one point, it is that the pretreatment of 7 days of levocetirizine resulted in substantially minimizing the injury to the lungs. The control group had total lung injury scores between 0-2, whereas 7 days of levocetirizine pretreatment diminished the damage caused by GPS injection (lung injury/animal test model of ARDS) so that the total lung injury scores were only slightly worse at 2-4. The GPS injected rat group showed very significant injury to the lungs when it was not protected with levocetirizine: total lung injury scores of 9-14.

**Potential Drug Trial Treatment of COVID-19 Inpatients using levocetirizine:**

We would need to secure a source of the drug and put it on hospital formulary.

Initiate 5 mg po Q12 hours x 2 when first suspect COVID-19.
This would get the drug steady state therapeutic levels quickly (within a day)

Maintenance dose of 5 mg po Q24 hours.

This medication could be given via NGT if needed (patient on ventilator/NPO).

Extend treatment to ER/drive through testing sites/primary care as the earlier we can start treatment, the more likely protective benefits may occur.

This would not significantly hamper the immune system but it would help prevent runaway damage by dampening the heightened immune response that occurs in some individuals.

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